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Differential Expression of Laminin Chains and Their Integrin Receptors in Human Gastric Mucosa

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The proliferating cells of the gastric mucosa are found among the pit and mucous neck cells. These cells migrate upward to renew the surface epithelium and downward to restitute the glandular cells. As the epithelial basement membranes (BMs) function as substrate for cell adhesion and migration as well as signals for their differentiation, we studied, by indirect immunofluorescence microscopy, the distribution of different laminin chains and their integrin receptors in adult human stomach. The immunoreactivity for laminin α2 chain localized to the BMs of glands and the lower parts of the gastric pits whereas the laminin α3 chain (laminin-5/kalinin) immunoreactivity was strictly confined to BMs underneath the surface epithelium and the upper parts of the pits. Proliferating mucosal epithelial cells, identified by Ki-67 antibodies, were confined to the areas containing both α2 and α3 laminin chains. The α1, β1, and γ1 laminin chains were found in all BMs of the mucosa whereas the β2 chain was prominent in mucosal blood vessels and also detectable in some glands. Among the laminin integrin receptors, the α3 and β4 subunits were seen to be expressed in cells along the BMs with the α3 laminin chain. The α6 integrin, on the other hand, was seen in all gastric epithelia. The present results demonstrate that in the adult human stomach laminin α2 and α3 chains show zonal distribution in BM underlying gastric mucosal epithelium whereas other laminin chains show a more general distribution. (Am J Pathol 1995, 147:1123–1132)

Epithelial basement membranes (BMs) are important determinants of cell differentiation, cell modeling, and tissue repair.[1,2] The protein constituents of BM, laminin, type IV collagen, and entactin as well as some proteoglycans function in these processes by interacting with other extracellular matrix proteins and with integrin receptors of the epithelial cell.[2–4] Numerous studies have provided evidence for a heterogeneity in BM composition during development and in adult tissues.[4–14]

Distinct functions can be attributed to laminin as a component of BMs. First, laminin provides substratum for adhesion and migration for cells equipped with distinct types of integrin receptors. On the other hand, laminin promotes differentiation as shown by inhibition of epithelial polarization during mouse nephrogenesis[15,16] by function-perturbing antibodies to the laminin α1 chain and by blocking the expression of lactase in co-culture of rat embryonal intestinal cells and fibroblasts[17] with anti-laminin antibodies. Structurally, laminin is a cross-shaped heterotrimeric protein consisting of one long arm chain variant (α1-α3) and two short arm chains (β1-β3, γ1–2) with at least seven known combinations (for the new nomenclature see Ref. 18).

The BMs of the gastrointestinal tract epithelium have been studied thus far mostly with respect to intestinal development and structure. Weiser et al[19] and Simon-Assman et al[20] have shown that both the epithelium and the mesenchyme play an important

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role in the production of intestinal BM constituents. Furthermore, it has been suggested that laminin in the intestinal BM slowly turns over throughout the entire crypt-villus axis,[21] that there are distinct differences in the expression of BM proteins during intestinal development,[22,23] and that in mature intestine there is an uninterrupted linear organization of BM proteins only at the base of the crypts.[23] Recent immunohistochemical studies have suggested a distinct reciprocity in the expression of laminin α1 and α2 chains along the crypt-villus axis in the human small intestine,[24,25] suggested to reflect the presence of distinct functional domains of the intestinal epithelium.

Little is known about the laminin composition of gastric BM. In the gastric mucosa the proliferating cells are located among the gastric pit and mucous neck cells from which they migrate both upward and downward to renew the surface epithelial and glandular cells, respectively.[26–33] The gastric mucosal BM seems to play a role in the high capacity for rapid repair of the surface epithelium after various injuries.[34–38] Here we show that in human gastric mucosa there is a distinctly reciprocal expression of laminin α2 and α3 chains in the BMs of surface and glandular epithelia, respectively, whereas the α1 chain is located at the BMs of both the surface and glandular epithelia. Among laminin integrin receptors, α3 and β4 subunits were predominantly expressed in cells abutting a BM with α3 laminin chain, with α6 integrin being expressed in all epithelia.

Materials and Methods

Tissue Samples

Tissue samples of adult human stomach, representing both uninvolved and involved gastric mucosa (cardia, n = 12; fundus, n = 10; and antrum, n = 14) were obtained either as biopsies taken during gastroscopy from patients at the Helsinki University Central Hospital or at gastric operations at the Helsinki University Central Hospital or at the Jorvi Hospital. The study was approved by the Ethical Committee of the Helsinki University Central Hospital. The tissues were immediately frozen in liquid nitrogen and stored at −80°C until used. All the specimens were reviewed by a pathologist after a routine hematoxylin and eosin staining.

Antibodies

The monoclonal antibodies (MAbs) against laminin α1 (4C7[39]), α2 (2G9; merosin[10,39]), β1 (3E5[39]), β2 (C9[9]), and γ1 (2E8[39]) chains have been characterized earlier in detail. The polyclonal antiserum against α3-chain-containing laminin-5[12] (formerly kalinin), MAb BM-2,[12] reacting with the 165-kd α3 subunit of laminin-5, and MAb BM-140[40] reacting with the 140-kD β3 subunit of laminin-5 have been described earlier. MAbs 3E5, 2E8, 2G9, and 4C7 were kindly provided by Dr. Eva Engvall and MAb C9 by Dr. Joshua Sanes. MAb AA3[41] against β4 integrin was kindly provided by Dr. Vito Quaranta, MAb J143[42] against α3 integrin by Lloyd J. Old, and MAb TS2/7[43] against α1 integrin by Dr. Martin E. Hemler. MAbs 10G11[44] against α2 integrin and GoH3[45] against α6 integrin were obtained from the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service (Amsterdam, The Netherlands). MAb 102DF5[46] against β1 integrin subunit has been characterized earlier. MAb Ki-67[47] (Dakopatts, Glostrup, Denmark) was used to assess the proliferative cells in the gastric mucosa.

Indirect Immunofluorescence

For immunohistochemical studies, 5-μm frozen sections were cut and fixed in acetone and precooled to −20°C. The sections were then exposed to the mouse or rat MAbs or to the polyclonal antiserum, washed in phosphate-buffered saline and exposed to the fluorescein isothiocyanate-coupled goat anti-mouse IgG, goat anti-rat IgG, or goat anti-rabbit IgG (all from Jackson Laboratories, West Grove, PA), respectively. In double immunostaining experiments, the specimens were first exposed to the mouse MAb followed by the fluorescein conjugate and to the rabbit antiserum followed by tetramethylrhodamine-coupled goat anti-mouse IgG antiserum (Jackson Laboratories). Omission of the primary MAb or replacement with an irrelevant MAb served as controls for immunostaining. The specimens were mounted in buffered glycerol and examined under a Leica Aristoplan microscope equipped with appropriate filters.

Results

The results are summarized in Table 1.

Laminin α-Chains in the Mucosa of Human Stomach

A bright immunoreactivity for the α1 chain of laminin was seen in the BM of the surface epithelium of cardiac (not shown), fundic (Figure 1a), and antral (Figure 1b) mucosa. It extended throughout the gastric pit region in all locations and was also detected

Table 1. *Distribution of Laminin Chains in the BM of Human Gastric Mucosa*

	α1	α2	α3	β1	β2	β3	γ1
Cardia							
Surface	++	−	++	++	−	++	+
Pit	+/++	−	+/−	++	−	+/−	+
Glands	+	++	−	++	+/−	−	+
Fundus							
Surface	++	−	++	++	−	++	+
Pit	+/−	−	+/−	++	−	+/	+
Glands	+	++	−	++	+/−	−	+
Antrum							
Surface	++	−	++	++	−	++	+
Pit	+	−	+/−	++	−	+/−	+
Glands	+	++	−	++	+/−	−	+
Capillaries	+	−	−	++	−	−	+
Vessels	+	(+)	−	++	++	−	+

+/−, interrupted or heterogenous; (+), weak; +, moderate; ++, prominent reactivity.

in the BM of the glandular structures deep in the mucosa. Immunoreactivity for the α1 laminin chain was also seen around the mucosal blood vessels and capillaries between the glands. Laminin α2 chain immunoreactivity, in contrast, was confined to the BM of glands and deeper parts of many gastric pits and was not detected in the BM of the surface epithelium (fundus, Figure 1c; deeper fundic glands, Figure 1d). Laminin-5 (kalinin)/α3 chain immunoreactivity, on the other hand, was strictly confined to the BM of mucosal surface epithelium and upper parts of the gastric pits in all three regions of the stomach as detected with the polyclonal antiserum (antrum, Figure 1e; fundus, Figure 1f) and MAbs BM-2 (α3 chain, not shown) and BM-140 (β3 chain, fundus, Figure 1g). The MAbs, in particular, gave a distinctly punctate staining pattern (Figure 1h). There was a distinct demarcation between the laminin-5-positive and -negative segments of the epithelium with the lower parts of the BM of gastric pits lacking the immunoreactivity. Additional double immunostaining experiments for laminin-5 with the polyclonal antiserum and for the β3 subunit with MAb BM-2 demonstrated that the two immunoreactivities coincided (not shown).

Double immunostaining experiments were carried out to compare the distribution of the laminin-5, as demonstrated with the rabbit antiserum, with that of laminin α1 and α2 chains visualized by MAbs. These experiments showed the distribution of laminin-5 in the surface epithelium and upper parts of the gastric pits, which was distinctly different from that of laminin α1 chain seen in all BMs (fundus: α3, Figure 2a; α1, Figure 2b; antrum: α3, Figure 2c; α1, Figure 2d) and that of laminin α2 chain confined solely to the BM of glands and deeper parts of gastric pits (fundus: α3, Figure 2e; α2, Figure 2f). Double immunostaining experiments with the MAb Ki-67, marking the proliferative cells by nuclear labeling, and antiserum to laminin-5 (fundus: α3, Figure 2g; Ki-67, Figure 2h) demonstrated that the proliferating cells were located to the lowest laminin-5 immunoreactive parts of the cryptal epithelium.

Laminin β1, β2, and γ1 Chains in Human Stomach

The BMs of both the surface epithelium and gastric pits and glands as well as capillaries were brightly immunoreactive for the laminin β1 chain (fundus, Figure 3a; antrum, Figure 3c) and the γ1 chain (fundus, Figure 3b). Immunoreactivity for the laminin β2 chain could be seen in the walls of the larger submucosal blood vessels as well as heterogeneously in the BM of some glands in the gastric mucosa (antrum, Figure 3d).

Integrin Laminin Receptors in the Stomach

We also studied the distribution of integrin laminin receptors in the gastric mucosal epithelium. A polarized, cell surface-confined immunoreactivity for the β1 integrin subunit was seen in the surface, pit, and glandular epithelial cells throughout the mucosa in all locations in addition to reactivity in stromal vessels and cells (fundus, Figure 4a). Immunoreactivities for the α1 and α2 integrin subunits were not seen in the mucosal epithelia, whereas a varying immunoreactivity was seen in stromal cells and vessels (α1, Figure 4b; α2, Figure 4c). In the epithelial cells, α6 integrin showed a distinctly polarized distribution (fundus, Figure 4d). Double immunostaining experiments for laminin-5 (Figure 4e) and the α3 integrin subunit (Figure 4f) and for laminin-5 (Figure 4g) and the β4 integrin subunit (Figure 4h), respectively, re-

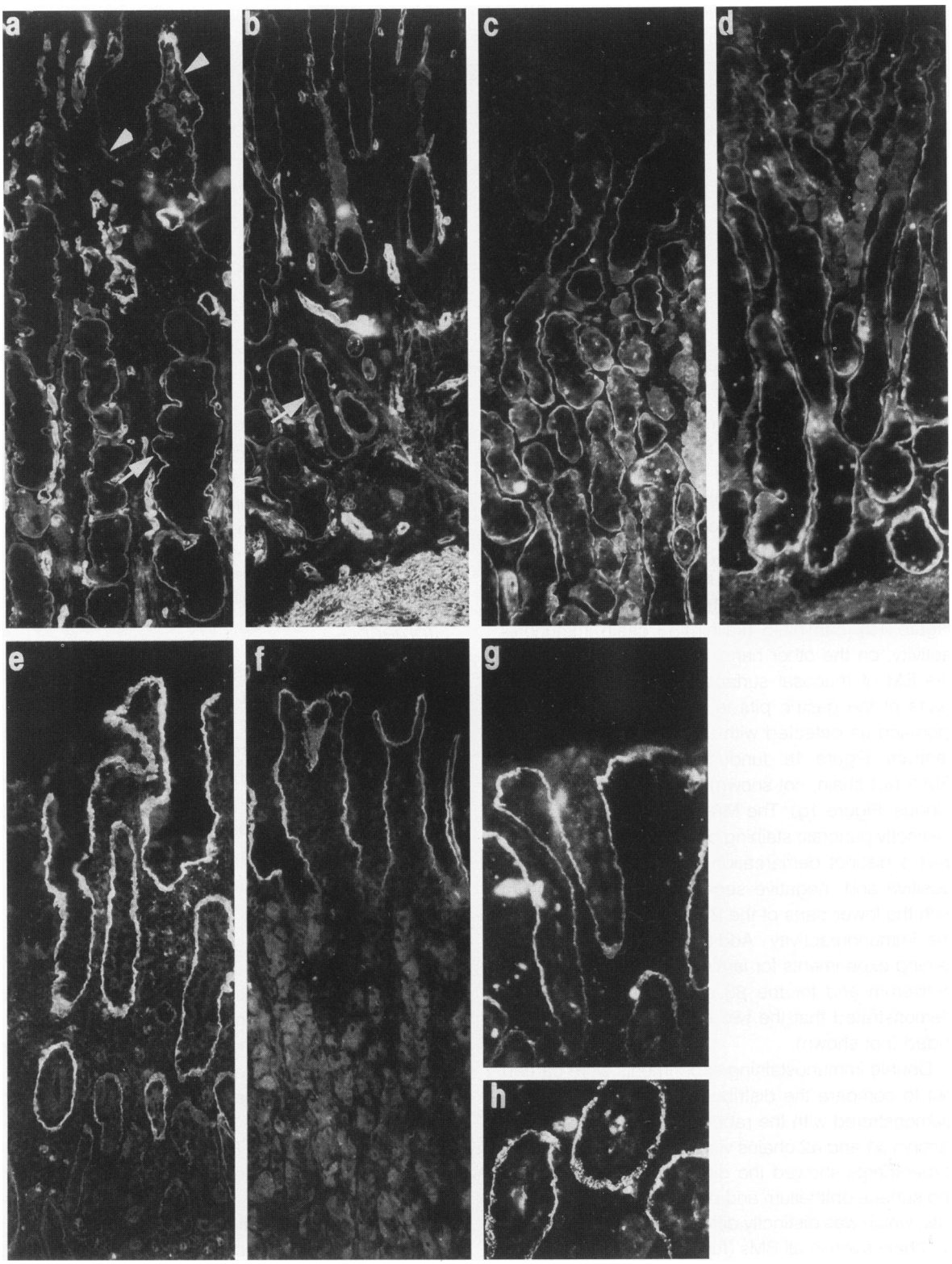

Figure 1. *Indirect immunofluorescence microscopy of fundic* (a) *and antral* (b) *mucosa for the laminin α1 chain. Note the reactivity of the BM of the surface epithelium* (arrowheads *in* a) *and glands* (arrows) *in both sites. The blood vessels and capillaries are also brightly reactive. Immunoreactivity for the laminin α2 chain is bright in deeper parts of gastric pits as well as in the BM of all glands in both the superficial* (c) *and the deeper part* (d) *of the antrum. In both the antrum* (e) *and the fundus* (f), *immunoreactivity with the polyclonal antiserum to laminin-5 is confined to the BM of the surface epithelium and the deeper parts of the gastric pits. Similar immunoreactivity is also seen with the MAb BM-140* (β3 *chain*) (g) *giving a punctate labeling at higher magnification* (h). *Original magnification,* ×250 (a–g); ×400 (h).

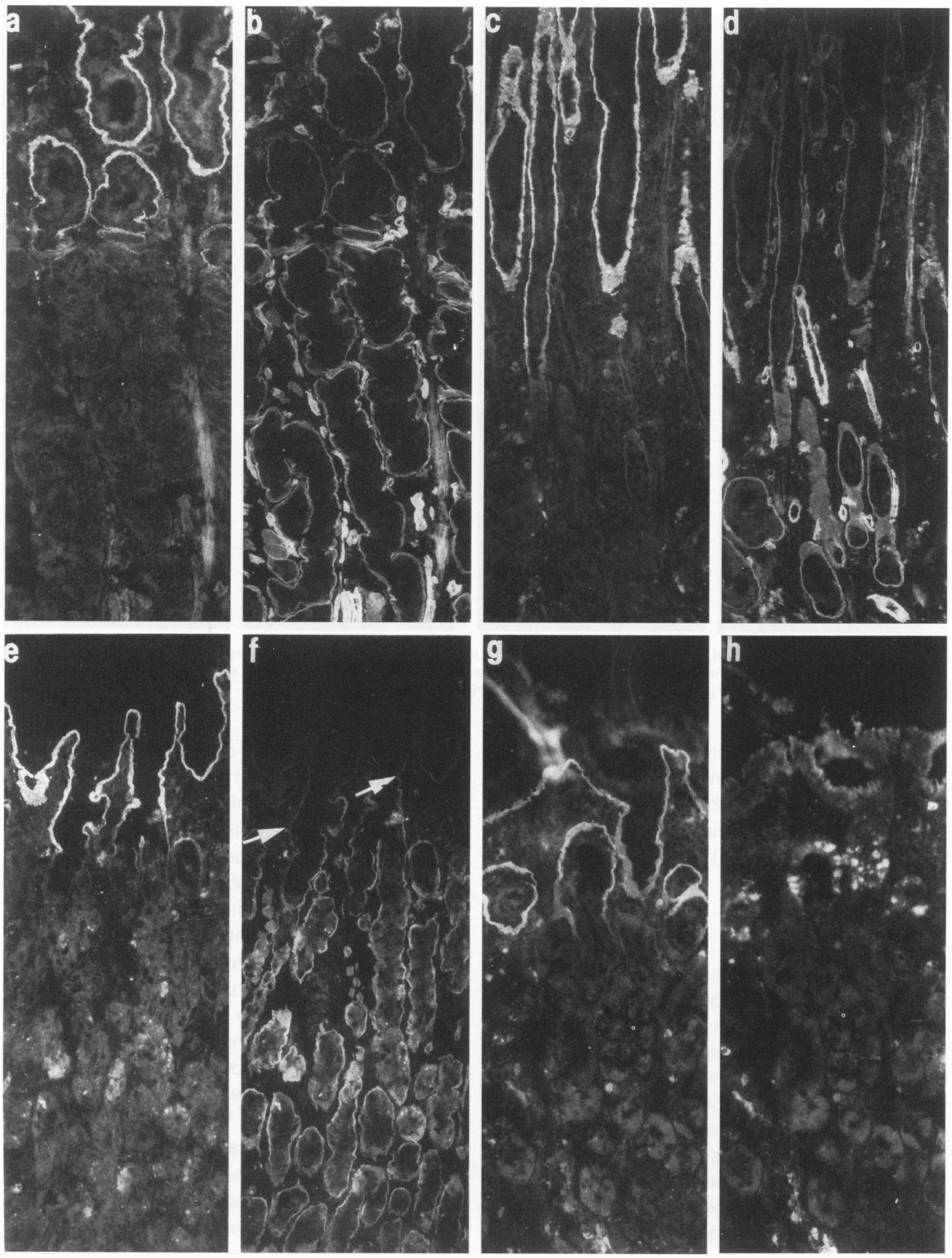

Figure 2. *Double indirect immunofluorescence staining of samples of human stomach for the laminin-5* (a, c, e, *and* g) *and for the* α*1 chain of laminin* (b *and* d), α*2 chain of laminin* (f) *and Ki-67 antigen for proliferating cells* (h). *In both the fundus* (a *and* b) *and the antrum* (c *and* d) *laminin-5 is confined to the surface epithelium and deeper part of the gastric pits, whereas laminin* α*1 chain immunoreactivity is also seen in all glands. In the fundus* (e *and* f) *the* α*2 chain of laminin is confined to the BM of glands and the deeper parts of gastric pits* (arrows *in* f) *whereas reactivity for laminin-5 is confined to the BM of surface epithelium and superficial parts of the gastric pits* (e). *Immunoreactivity for proliferative cells with MAb Ki-67* (h) *is seen in the deeper parts of the gastric pits and the upper parts of glands corresponding to the strongest labeling for laminin-5 chain* (g). *Original magnification,* ×*240.*

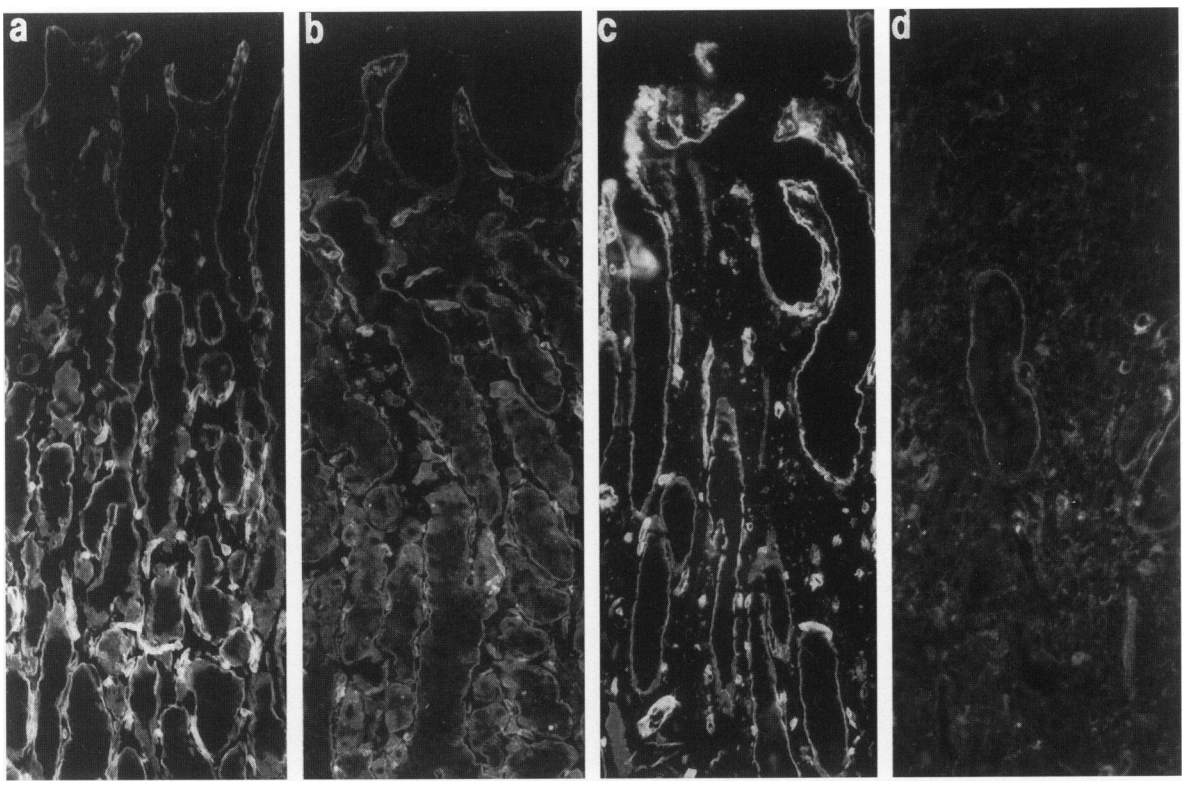

Figure 3. *Immunoreactivity for the β1 laminin chain is seen throughout the BM of the fundus* (a) *and the antrum* (c) *and similar immunoreactivity is seen in all BMs for the γ1 laminin chain in the fundus* (b). *Immunoreactivity for the laminin β2 chain is mostly confined to blood vessels but is also faintly seen in the BM of some glands in the antral mucosa* (d). *Original magnification, ×240.*

vealed that immunoreactivities for both of these integrin subunits and the laminin-5 closely coincided in the fundus as well as in other parts of the stomach. Capillaries were clearly immunoreactive for the β4 integrin subunit (Figure 4h).

Discussion

The present results show that laminin composition of the gastric BMs is heterogeneous and that laminin distribution coincides with distinct domains of the gastric epithelium. Thus, laminin chains corresponding to the α1-β1-β2 laminin-1 heterotrimer, ie, the classic Engelbreth-Holm-Swarm tumor laminin,[9,18] presented a widespread expression throughout the mucosal epithelium. In BMs of the surface epithelium and glands, on the other hand, expression of α3 and α2 chains of laminin, respectively, were also seen. Interestingly, whereas α2 and α3 laminin chain immunoreactivities were grossly mutually exclusive, they were also partially overlapping. Thus, it appears that BMs of the deep parts of gastric pits and the uppermost glands could express three different types of laminin heterotrimers: laminin-1, -2, and -5. The double-labeling results demonstrated a co-localization of α3 and β3 chains of laminin in the surface epithelium. Thus, in addition to laminin 1, it may also express both laminin-5 (α3β3γ2) and laminin-6 (α3β1γ1) but not only laminin-6.

The regular renewal process of the gastric epithelium appears to consist of cell proliferation in the gastric pits and upper parts of the glands giving rise to epithelial cells migrating upward to the surface epithelium and downward to the glandular epithelium as shown by autoradiography[28–30,37,48,49] and more recently by MAb Ki-67 immunohistochemistry.[27,33] Many studies have shown that the gastric surface epithelium rapidly recovers from various injuries caused, for example, by alcohol or other chemical insults.[35,37,50–53] The recovery process begins with a rapid spreading and migration of the viable marginal epithelial cells to cover the denuded surface with the cell division and only later supplying more cells for the recovery process.[34] Both *in vivo* and *in vitro* studies have suggested the importance of protein tyrosine kinases[48,50] and extracellular matrix, especially the BM proteins, in this process.[36,54]

In intestine, the composition and possible functional implications of BM laminins have been studied in more detail. These studies have shown a differen-

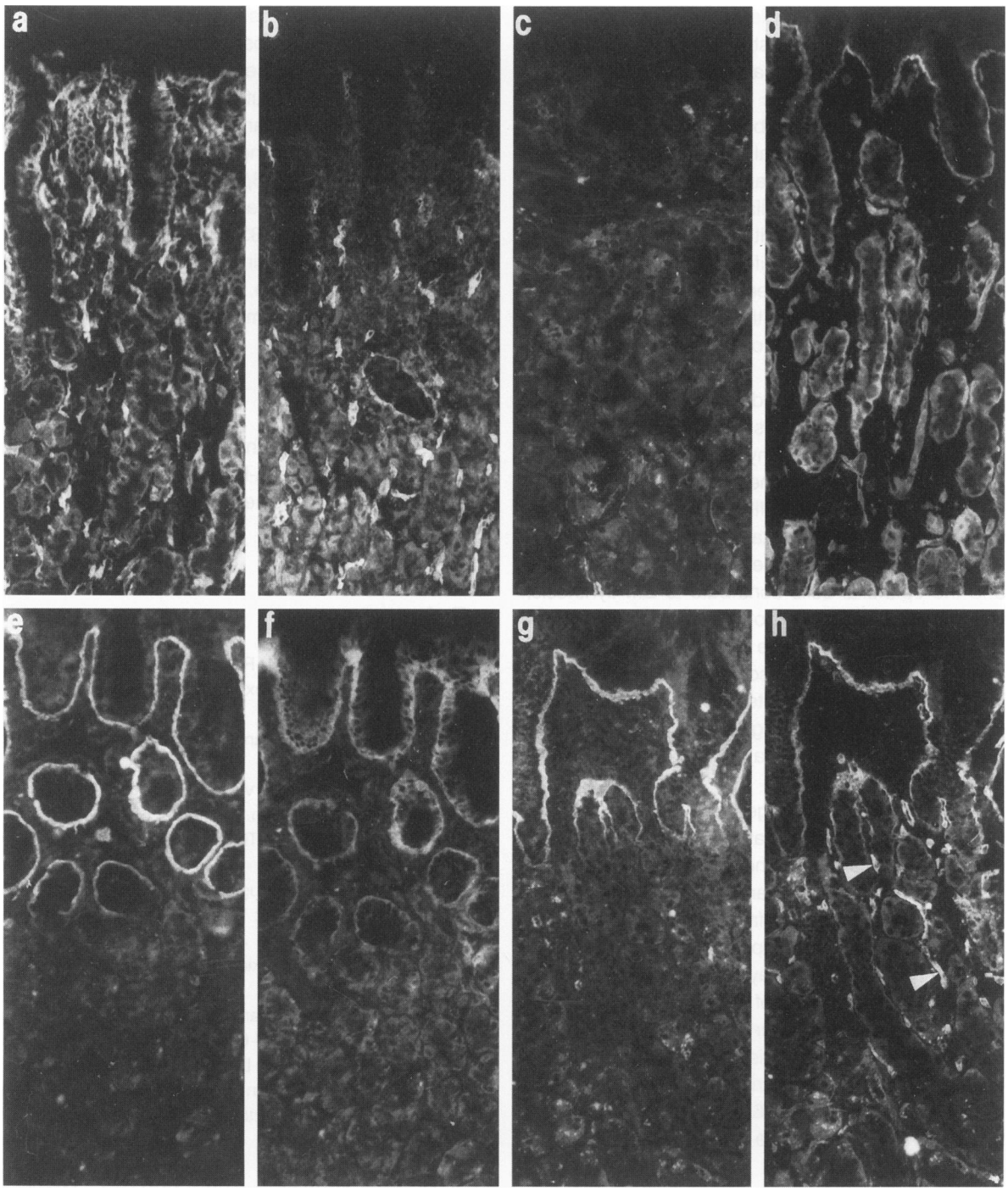

Figure 4. *Immunoreactivity for the integrin β1 subunit shows a polarized distribution in all the surface epithelial and the glandular epithelial cells and is also seen in capillaries (fundus,* a). *Immunoreactivity for the α1 integrin subunit was confined to stromal capillaries (fundus,* b) *and only a faint immunoreactivity for the α2 integrin subunit was seen (fundus,* c). *Immunoreactivity for the α6 integrin subunit was seen in a basally polarized manner in all epithelial cells and the mucosa (fundus,* d). *In double immunostaining experiments, immunoreactivities against both integrins α3* (f) *and β4* (h) *were co-localized with that of laminin-5* (e *and* g). *Capillaries were clearly immunoreactive for the integrin β4 subunit* (arrowheads *in* h). *Original magnification, ×240* (a–d); *×300* (e–h).

tial and reciprocal expression of laminin α1 and α2 chains in crypts suggesting that differential laminin composition in various parts could provide guidance, eg, for the renewal of intestinal epithelium from the crypts.[24,25] Unlike in intestine, in stomach, laminin α1 chain does not seem to be restricted solely to the BM of the gastric surface epithelium. Instead, laminin α1 chain was found throughout the BMs of the gastric mucosa. On the other hand, the α3 and β3 chains of laminin, which were not investigated in

the above mentioned studies on intestine, appeared to be restricted in their distribution to the BM of the gastric surface epithelium as well as to the BM of the upper parts of the gastric pits. Furthermore, in the present study, double-labeling experiments confirmed the nearly reciprocal but partially overlapping distribution of laminin $\alpha 3$ and $\alpha 2$ chains in the surface and glandular epithelia, respectively. Although double-labeling studies with the MAb Ki-67, widely used as a marker for proliferating cells,[55] could be carried out only with respect to the laminin-5, these results clearly suggested that the proliferative cells are confined to the area of overlapping expression of $\alpha 2$ and $\alpha 3$ laminin chains.

In several previous studies, it has been speculated that the $\alpha 2$ laminin subunit in BMs would be predominantly of mesenchymal origin.[25,56,57] In the intestine this is based on the observation that there is a specific type of cryptal fibroblast in close association with $\alpha 2$-laminin-containing cryptal BM.[25] It is known that in the intestine both the mesenchymal and the epithelial cells contribute to BM synthesis, including the production of laminins.[19] However, it should be noticed that the $\alpha 2$ chain of laminin was seen in the stomach in association with all glandular BMs instead of, as in the intestine, in a very restricted localization. This result suggests to us that the epithelial cells may be the major source of this laminin chain in the stomach.

The present results suggest that cell differentiation in the stomach mucosa may involve cell recognition of distinct BMs that may then contribute to the specific differentiation program of mucosal epithelial cells either toward cell surface or glandular differentiation, respectively. The specific composition of the surface epithelial BM may also contribute to the rapid recovery capacity of the gastric surface epithelium after chemical injury.

There are at least four distinct integral cell surface laminin receptors in human epithelial cells: the integrins $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 6\beta 4$, and $\alpha 6\beta 1$.[2–4] Among them $\alpha 3\beta 1$ and $\alpha 6\beta 4$ have been suggested to bind not only to the classical Engelbreth-Holm-Swarm tumor-laminin-1 but also to laminin-5.[58,59] Notable, however, is that it is still unresolved whether the different laminins reflect distinct functional properties, as cell culture studies have not supported this possibility.[6] Based on cell culture studies it has been suggested that laminin isoforms are differentially recognized by distinct cell surface integrin receptors, suggesting that distinct integrins may determine the ability of cells to adhere to BMs that differ in composition.[60] The present results suggest that in the stomach mucosa the surface epithelial and part of the gastric pit epithelial cells express the $\alpha 6\beta 4$ and $\alpha 3\beta 1$ integrin complexes closely confined to BM areas containing laminin-5 whereas the $\alpha 6\beta 1$ integrin complex is found throughout the epithelium. Other laminin binding integrins are not found in the gastric mucosal epithelium. These results therefore imply that cells acquiring $\alpha 3\beta 1$ and $\alpha 6\beta 4$ integrins are directed toward mucosal surface differentiation mediated by laminin-5 ($\alpha 3\beta 3\gamma 2$) and laminin-1 ($\alpha 1\beta 1\gamma 1$) whereas those acquiring $\alpha 6\beta 1$ integrin undergo glandular differentiation, perhaps mediated by laminin-2- ($\alpha 2\beta 1\gamma 1$) and laminin-1-containing BM.

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